

Are N-of-1 Trials an Economically Viable Option to Improve Access to Selected High Cost Medications? The Australian Experience

Paul A. Scuffham, PhD, PG, Dip, BA,¹ Michael J. Yelland, MB, BS, PhD, FRACGP, FAFMM,¹ Jane Nikles, MBBS,² Eva Pietrzak, PhD,³ David Wilkinson, BSc(Hons), MBChB, MSc, MD, PhD, DSc, FRACGP, FAFPHM, MRCP⁴

¹School of Medicine, Griffith University, Meadowbrook, Qld, Australia; ²School of Medicine, The University of Queensland, Herston, Qld, Australia; ³School of Population Health, The University of Queensland, Herston, Qld, Australia; ⁴School of Medicine, The University of Queensland, Herston, Qld, Australia

ABSTRACT

Objective: To explore the economic viability of N-of-1 trials for improving access to selected high cost medications in Australia.

Methods: Cost and effectiveness estimates were derived from two N-of-1 trials conducted by The University of Queensland from 2003 to 2005—celecoxib versus sustained-release paracetamol for osteoarthritis in a general practice setting and gabapentin versus placebo for chronic neuropathic pain in a hospital setting. Effectiveness was determined by the proportion of responders to each medication. The costs of trials were offset against the savings generated by subsequent changes in prescribing. Decision analysis models with semi-Markov processes were used to compare different scenarios of N-of-1 trials versus usual care.

Results: The fixed cost of performing N-of-1 trials was approximately AUS\$23,000 for each trial and the variable cost was approximately AUS\$1300 per participant. Clinical outcomes favored celecoxib over paracetamol in 17% of

participants and gabapentin over placebo in 24% of participants. Modeling these results showed that the cost-offsets from efficient use of medications were less than the cost of running a trial; however, the incremental costs per quality-adjusted life-year gained were AUS\$6,896 and AUS\$29,550 for the gabapentin/placebo and celecoxib/paracetamol trials, respectively, over a 5-year horizon. Key factors affecting the viability were the time horizon modeled, the variable cost per participant, the probability of response to the intervention medication, and rates of use in nonresponders and the usual care alternative.

Conclusions: The N-of-1 strategy offers a realistic and viable option for increasing access to selected high cost medications where the medications are used for the symptomatic treatment of chronic disease, have rapid onset of action, and clinical response is unpredictable without a trial.

Keywords: celecoxib, chronic neuropathic pain, cost-effectiveness, gabapentin, N-of-1 trials, osteoarthritis.

Introduction

Over the last 10 years there has been increasing concern about the high psychosocial, economic and health costs of inappropriate medication use. In Australia, the Pharmaceutical Benefits Scheme (PBS) is the government scheme that subsidizes common prescription medications. The growth of Government expenditure on subsidized medications listed on the PBS is of increasing concern. For the year ending 30 June 2004 PBS expenditure totaled AUS\$5 billion, a 9.3% increase compared with the previous year [1]. In the same period, total PBS prescription volumes increased only by 4.3%.

Address correspondence to: Michael J. Yelland, School of Medicine, Logan Campus, Griffith University, University Drive, Meadowbrook, Qld, Australia. E-mail: m.yelland@griffith.edu.au
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There is a need to control government expenditure while still making medications available to those in whom they will be effective. Consequently, recommendations for listing of medications on the PBS by the Pharmaceutical Benefits Advisory Committee (PBAC) are heavily based on high-level evidence from randomized controlled trials. Typically these trials define the mean response in a group of participants; however, the variation in response within these groups may be large and it may be impossible to predict response at the individual level. It is well known that drug trials can be performed on younger and/or healthier sufferers of a particular disease and there can be differences between the trial groups and the ultimate target groups of a given medication, for example, [2,3]. Evidence from population-based trials may result in the long-term prescription of expensive medication to individuals for whom it is not effective or even harmful, leading to suboptimal cost-effectiveness and wastage of resources.

When applying economic data within a formal approvals process, such as that used by the PBAC, an overall estimate of the incremental cost per unit of health benefit gained is provided in the form of the incremental cost-effectiveness ratio—ICER, effectively averaging across responders and nonresponders. In reality the cost to gain a unit of health benefit among responders will be very low whereas that among nonresponders will be very high. What options then exist for more effective “targeting” of drug treatments, especially in the era of very high cost medications, which may offer marginal benefits to a large group (but very high benefit to small numbers of patients), and may also have significant side effects?

Current targeting strategies may be less than optimal because they rely on identifying characteristics of groups of patients who are likely to have a higher response rate. Nonresponders are still included in this target group and potential responders may be excluded. For a few medications, genetic testing to identify potential responders is becoming important; however, this approach is currently limited. For some medications, such individualized targeting can only be obtained through N-of-1 trials. N-of-1 trials provide empirical data of individual responses to treatment. These are within-patient randomized, double-blind, cross-over comparisons of two treatment regimens (one of which may be placebo), in which patients act as their own controls [4]. The N-of-1 trial offers the highest level of evidence for the individual on the effectiveness of long-term medications used for symptomatic treatment of stable chronic conditions [5].

The use of N-of-1 trials in routine prescribing could potentially produce financial savings, depending on five factors: the cost of the medication, the duration of use of the medication, the proportion of responders, the proportion of nonresponders who continue medication and the cost of undertaking the trials. Potential financial savings to the PBS are likely to be greater where response rates are relatively low. If nonresponders cease their medication, morbidity and mortality from medication-related adverse events, and costs to the health-care system would be greatly reduced. Early identification of nonresponders has the potential to reduce the cost per unit of effect gained in responders, improving the cost-effectiveness of the medication. It shifts resource allocation decisions to the level of the individual patient—to the margin [6].

A thoughtful article by Karnon discusses the potential of N-of-1 trials in the estimation of individualized cost-effectiveness and uses hypothetical examples [6]. Larson et al. ran an N-of-1 trial service from 1991 to 1993 in the United States [4]. Crude estimates of resource consumption including time-motion studies estimated that total costs per trial would likely be \$400 to \$500 in 1990 US dollars. They did not calculate

savings that might result from the trials that led to discontinuation of chronic medications or the avoidance of side effects. Guyatt and colleagues who also offered an N-of-1 trial service in the United States found that a substantial proportion of trials resulted in discontinuation of medication that would otherwise have been continued for months or years [7].

Until now there has been only one report of a formal economic evaluation of N-of-1 trials. This is a recent randomized controlled trial from Canada, which showed that N-of-1 trials with diclofenac/misoprostol produced slightly better health outcomes (as measured by the Health Assessment Questionnaire for pain and disability, WOMAC scales, and physician global assessments), although were more time-consuming and expensive over a relatively short time horizon (6 months), than standard treatment in osteoarthritis (OA) (cessation of NSAID with commencement if symptoms worsened) [8]. This small study had some important limitations. The numbers were small—there were 25 patients in one group and 24 in the other and there was a high dropout rate from the N-of-1 trial group (18 out of 24 did not complete 3 crossovers). The higher costs for the N-of-1 group (from US\$60 to \$160 more per patient) were due to higher costs of medications, nurse and physician time, and travel costs.

Our study aimed to determine the economic viability of N-of-1 trials of medications for symptomatic treatment of stable chronic conditions in the Australian context, in both hospital and community settings.

Methods

In 2003 to 2005, the N-of-1 trial service at The University of Queensland conducted two N-of-1 trials. The first compared celecoxib with sustained release paracetamol (SR paracetamol) for osteoarthritis and was performed in general practices throughout Australia. The second compared gabapentin with placebo for chronic neuropathic pain and was performed in outpatient clinics in two Australian hospitals.

The duration of each trial was 12 weeks, comprising three 4-week cycles with a fortnight on each medication assigned in a random order (e.g., 2 weeks of celecoxib followed by 2 weeks of SR paracetamol). The choice of three pairs of treatment periods is regarded as the best compromise between statistical certainty and patient acceptability. With one pair, the chance of a false positive or false negative result is up to 50%, but with three pairs this reduces to 12.5%. More than three cycles makes the trials unacceptably long and expensive. Trials could be stopped early in cases of severe adverse reactions or if symptoms became intolerable.

Patients were randomized to their starting medication in blocks of four. Five variables were monitored in each cycle—pain, stiffness (for celecoxib/paracetamol trials) or sleep interference (for gabapentin/placebo trials), functional limitation, frequency of adverse events, and preferred medication. Differential responses in pain, stiffness, sleep interference and functional limitation responses were determined by minimum clinically detectable differences [9–11] for adverse events by a lower frequency on one medication in at least two cycles and for medication preference by a preference for one medication in at least two cycles. The overall response status of each patient was then based on an equal weighting of the differential response for each variable [12,13]. Participants and their doctors were sent a comprehensive report of the results within 2 weeks of completion of the last cycle. This was used to inform, but not dictate, future medication usage. Ethics approval for both trials was obtained from The University of Queensland's Medical Research Ethics Committee, and additionally, for the gabapentin versus placebo trial, from the ethics committees of the participating institutions, Princess Alexandra Hospital, Brisbane and the Port Kembla Hospital. Because of the increased risk of sudden death from celecoxib, in late 2004 the Therapeutic Goods Administration instructed all trials using celecoxib to cease—including ours.

The economic evaluation of these trials is primarily a cost-minimization analysis. This approach was chosen because medication and resource use were routinely measured during follow-up, but health outcome data were monitored during the trial period only; thus a full economic evaluation was not possible. Nevertheless, we address this shortcoming by undertaking cost-effectiveness and cost-utility analyses by extrapolating the pain scores for responders and nonresponders from the trial for the time horizon modeled. The pain index was recorded on a visual analog 0–10 scale with 0 (no pain) and 10 (extreme pain); scores were categorized and converted to a utility weight to estimate quality-adjusted life-years (QALYs). Although not ideal, this approach does give some relativity to the cost minimization analysis by estimating the incremental cost per point decrease on the pain scale and the incremental cost per QALY gained.

Cost of N-of-1 Trials

We estimated the costs of setting up and running a fully funded university-based N-of-1 trials service based on our experience with the staff time and costs of running the N-of-1 trials funded from research grants from 2003 to 2005. All costs are expressed in Australian dollars. Costs included a fixed component for trial establishment that is independent of the number of patients in a trial, and a variable component per patient for each N-of-1 trial. The fixed establishment

costs were estimated at \$23,280 per trial. These comprised staff costs for protocol development (\$8130), funding applications (\$4730), ethics applications and business agreements (\$3000), preparation of forms and questionnaires (\$4350), database development (\$2200) and design/preparation of medication packs (\$870). The costs of N-of-1 trials per patient included the costs of recruitment, administration, data collection and analysis, generation and feedback of results and 12 months follow-up of health and economic outcomes. These totaled \$610 for each patient for the celecoxib/paracetamol trial and \$577 for each patient for the gabapentin/placebo trial.

Because the N-of-1 trials are an ongoing service, only a proportion of the total fixed costs can be assigned to those who have participated so far. Therefore, for the fixed costs, we have assumed the protocol will be valid for 200 participants in each trial, and calculated a fixed cost per patient of \$116 based on this number. The fixed costs and patient trial costs were subject sequentially to the university infrastructure charge of 50%, a surcharge of 20% for internal infrastructure and then the statutory goods and services tax of 10%. In this scenario, the total cost per patient is set at \$1373 for celecoxib/paracetamol trials and \$1438 for gabapentin/placebo trials. These costs, and the number of participants, are later varied in a sensitivity analysis.

Modeling

Structure of the model. A decision analysis model with two arms: “N-of-1 trial” and “No trial” was constructed using TreeAge Pro Software [14]. Within the N-of-1 arm, there is a chance (probability) that the intervention medication (celecoxib and gabapentin) is better than the alternative medication. The alternative medication for each trial is the set of other medications used by participants, for example, analgesics (including paracetamol), opioids, and nonsteroidal anti-inflammatory drugs. These alternatives are used for the economic evaluation, rather than placebo in the gabapentin trial and paracetamol in the celecoxib trial, because participants used these medications for pain rescue during the trial and used these before and/or after the trial during follow-up. Within each arm of the model, there are five “health states” based on the observed pattern of medication use and the probability of survival. The health states are: intervention medication only, intervention plus other medications, other medications only, no medications, and dead. Using a semi-Markov process with monthly cycles, patients transition between medications or can die (at the Australian age-specific all-cause mortality rate [15]). This approach allows “leakage” of those shown to be non-responsive to the intervention medication to use the intervention medication, and vice versa. The “No trial”

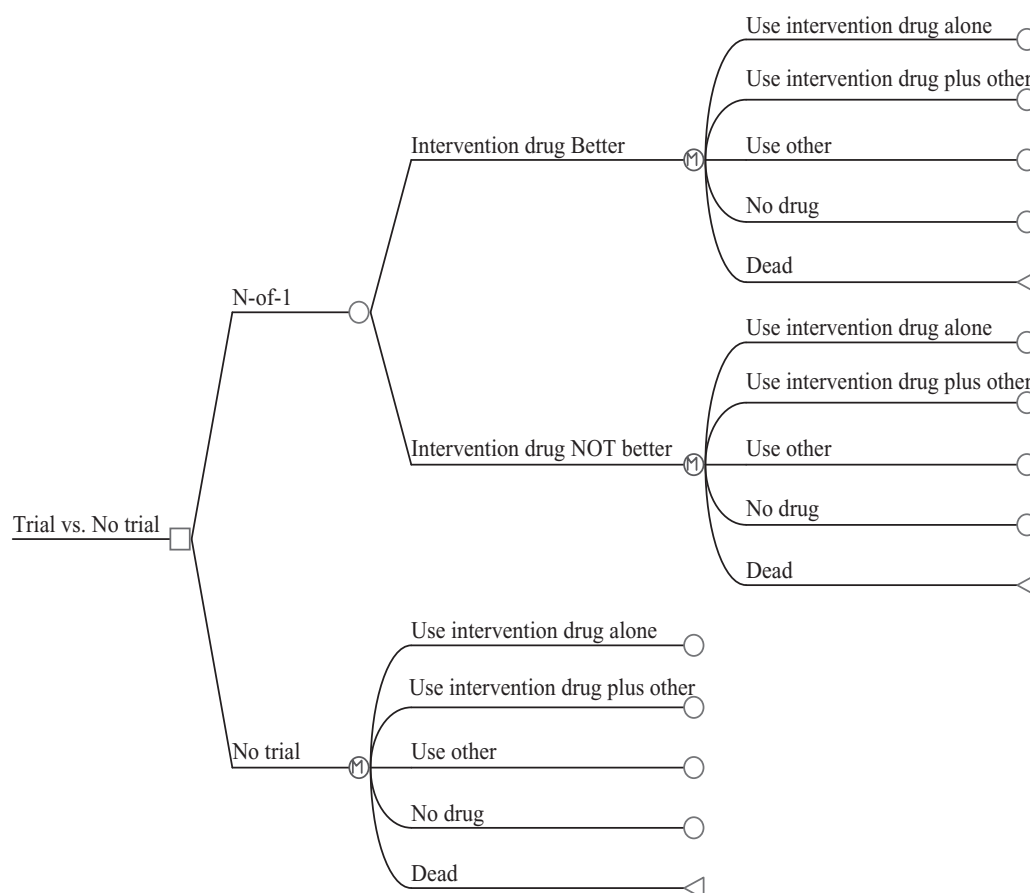


Figure 1 Illustration of the Decision Model with medication use/health states.

comparator follows the same pathway but without testing of which medication is best. The model used for the evaluation of both trials is summarized in Figure 1.

Assumptions used in the base-case model

1. Response status is defined by an equal weighting of the differential response five outcomes: pain, functional limitation, adverse event frequency and preferred medication for both trials as described earlier in the methods. Responders are defined as those showing a superior response to celecoxib compared with SR paracetamol or gabapentin compared with placebo.
2. Those participants showing no difference between medications or a superior response to SR paracetamol or placebo are defined as nonresponders and would continue on SR paracetamol or no additional medication, respectively.
3. Response rates used in estimates are those from the series of completed trials conducted for this project (i.e., 17.1% for celecoxib and 24.0% for gabapentin) [12,13].
4. The use of the intervention medication by Responders is that observed in the 12 months of follow-up from the trials; the rates of use of the intervention medication only, intervention medication in combination with other medication, and other medication are constant.
5. Nonresponders are allowed to continue use of celecoxib or gabapentin in the N-of-1 arm but, because participants are informed of their response outcome, they discontinue use of the intervention medication at a rate of 50% annually.
6. Medication use in the no-trial arms is estimated from the trial data. For the celecoxib/paracetamol analysis, the pretrial data on medication use were used; for the gabapentin analysis, we assumed the use of gabapentin was double that observed for nonresponders over the 12-months follow-up. This assumption was made because pretrial data indicated very low use of gabapentin. The expected use of gabapentin in the absence of a trial is much greater than reported for the pretrial period because all patients are expected to use gabapentin for an unknown period (NB: patients were recruited into the N-of-1 trial when the clinician considered a trial of gabapentin). In the absence of a trial some would respond and others

would persist with using it even in the absence of a true response.

7. An annual discontinuation rate of 25% of the intervention medication is used in the no-trial arm.
8. Compliance with medications is 100%.
9. The full dispensing price for all medications (as per the PBS Schedule) is used.
10. The pain scores used for responders, and consequently utility weights, are the mean scores reported by responders when using the intervention medication. For nonresponders, the mean scores of intervention and comparator medication are used, and for the no-trial arm, the mean of the all scores (intervention and comparator medication for responders and nonresponders) is used.
11. The pain scores were mapped to the EQ-5D by categorizing scores as no pain or discomfort ≤ 1 ; moderate pain or discomfort ≤ 6 , and extreme pain or discomfort > 6 . To approximate a utility weight, the EQ-5D scoring algorithm for the UK was used [16] with the assumption that there were no problems with mobility, personal care, usual activities or anxiety/depression.
12. The pain score and utility weight are constant for the duration of the time horizon modeled.

Variables used in the models. The proportions using each medication are calculated from the N-of-1 trials using the means over 12 months' follow-up. Upper and lower values were calculated from the 95% confidence intervals. Similarly, costs for each medication were calculated from observed medication usage over 12 months. This approach implicitly accounts for different daily doses. The mean costs, and 95% confidence intervals are used for the upper and lower values. The time horizon used in the base-case model is 5 years and is varied in sensitivity analyses up to end of life. All costs (and QALYs) are discounted at 5% [17]. Variables used in the models are presented in Tables 1 and 2.

Sensitivity and Scenario Analyses

One-way sensitivity analyses were performed on all variables to identify the variables that have the greatest impact on the incremental costs and the incremental cost per QALY gained for both models, including assessing the effects of scale on cost-effectiveness. A scenario was developed to assess a policy where high cost pharmaceuticals require that an individual's response must be proven through an N-of-1 trial before the medication is approved for government subsidy to that individual. In addition, an analysis of responders compared with nonresponders is presented. This analysis is equivalent to an evaluation of the

efficacy and costs of an intervention medication compared with the control. Incremental costs and QALYs are estimated for the intervention medication.

Results

Within the range of parameters chosen for the base-case models, the "N-of-1 trial" option costs significantly more per person than the alternative of "No trial" for both trials conducted. Nevertheless, the cost of the trial was partially offset by more efficient use of medications through nonresponders using less of the high cost medication. These cost-offsets were greater for the gabapentin/placebo trial (\$569) than for the celecoxib/paracetamol trial (\$221), resulting in incremental costs of \$869 and \$1152 for the two trials, respectively (Table 3).

The pain scores, measured during the trials only, show that the average level of pain for participants in N-of-1 trials was reduced by 0.278 and 0.113 points for the gabapentin/placebo and celecoxib/paracetamol trials compared with the "No trial" alternative. Thus, an N-of-1 trial can reduce pain through efficient medication use. Although these reductions in pain score may appear small, they contain the scores from responders and nonresponders.

Converting the pain scores into utility weights, and then to QALYs, the N-of-1 trials lead to an additional 0.126 QALYs for the gabapentin/placebo trial and 0.039 QALYs for the celecoxib/paracetamol trial over 5 years compared with no trial.

The incremental cost per one-point reduction on the 10-point pain scale is \$3,125 and \$10,199 for the gabapentin/placebo and celecoxib/paracetamol trials, respectively, and the incremental cost per QALY gained is \$6,896 and \$29,550, respectively.

Sensitivity Analyses

Varying the time horizon modeled shows that greater cost-offsets are achieved with longer horizons (i.e., the incremental cost is smaller) for both trials; similarly, the QALYs gained also increase with increased time horizons. Using a horizon to the end of life, the ICERs were \$1,725 and \$10,278 per QALY gained.

Tornado diagrams are used to depict the change in expected costs from changing individual parameter values within their expected range (Tables 1 and 2); the factor that has the greatest effect is depicted at the top of the diagram down to those with the smallest effect on results. Tornado diagrams are presented for the incremental costs for each trial (Figs. 2 and 3) and the incremental cost per QALY gained (Figs. 4 and 5) using the 5-year time horizon.

For both N-of-1 trials, the rates of use of the intervention medication in the no-trial alternative and the nonresponders were highly important factors affecting

Table 1 Variables used in the celecoxib/paracetamol model

Variable	Base-case value	Lower value	Upper value	Notes
Cost of trial				
Total fixed costs (\$)	23,200	11,800	39,600	Based on actual staff inputs and infrastructure costs
Variable cost per patient (\$)	1,257	628	1,500	
N participants	200	50	2,000	
Celecoxib responders				
Proportion celecoxib better	0.171	0.085	0.320	Celecoxib/paracetamol N-of-1 trial; lower and upper 95% CI; mean at 12 months f/u
Use celecoxib only	0.194	0.158	0.231	
Use celecoxib and other meds	0.278	0.167	0.388	
Use other meds only	0.333	0.278	0.389	
No meds	0.194	0.146	0.243	
Celecoxib nonresponders				
Use celecoxib only	0.083	0.000	0.093	Celecoxib/paracetamol N-of-1 trial; lower and upper 95% CI; mean at 12 months f/u
Use celecoxib and other meds	0.185	0.000	0.206	
Use other meds only	0.667	0.533	0.800	
No meds	0.065	0.064	0.067	
Celecoxib discontinuation rate (annual)	0.500	0.000	1.000	
No trial				
Use celecoxib only	0.089	0.000	0.691	Celecoxib/paracetamol N-of-1 trial; lower and upper 95% CI; pretrial usage
Use celecoxib and other meds	0.375	0.309	0.691	
Use other meds only	0.500	0.000	0.750	
No meds	0.036	0.000	0.072	
Celecoxib discontinuation rate (annual)	0.250	0.000	0.500	
Other factors				
Cost of celecoxib (\$)	34.74	9.89	59.59	Calculated from observed daily doses over 12 months f/u, using PBS costs; lower and upper 95% CI
Cost of other meds (\$)	17.90	8.32	44.12	
Cost of celecoxib plus other meds (\$)	39.86	20.90	58.82	
Pain score celecoxib responder	3.89	3.19	4.59	Mean score of responders for periods of gabapentin use during trial; lower and upper 95% CI
Pain score celecoxib nonresponder	4.55	4.20	4.89	Mean score of nonresponders during trial; lower and upper 95% CI
Pain score no trial	4.55	4.25	4.85	Mean from all in trial; lower and upper 95% CI
Utility—celecoxib responder	0.78	0.47	1.00	Calculated from proportion with no, moderate, and extreme pain mapped to the EQ-5D
Utility—celecoxib nonresponder	0.67	0.64	0.71	
Utility—no trial	0.68	0.65	0.71	
Probability of death	Age-specific mortality rates			[15]
Start age (years)	64.2	54.2	74.2	Observed in trial; lower and upper 95% CI
Duration (months)	60	12	End of life	
Discount rate (annual)	5.00%	0.00%	10.00%	[17]

CI, confidence interval; meds, medications.

the incremental costs and ICERs. That is, the probability of use of the intervention medication by nonresponders and without a trial makes a substantial difference to the costs.

The variable costs to conduct N-of-1 trials were a key driver of the costs and ICERs in all four tornado diagrams. Assumption of economies of scale were obtained, the variable costs could be reduced by approximately 50% for the celecoxib/paracetamol trial and 40% for the gabapentin/placebo trial; this would result in incremental costs and ICERs that are 47% and 44% lower compared with the base case. The costs of the intervention medications had relatively little effect on the incremental costs or ICERs; more important was the cost of the alternative medications used—both in combinations with the intervention medication and without the intervention medication. When lower “other” medication costs were used, the incremental costs and the ICERs increased as the difference in costs between running an

N-of-1 trial and the alternative were greater. As such, the benefits of N-of-1 trials were reduced.

Changes in the probabilities of responding to celecoxib in the celecoxib/paracetamol trial had little effect on the incremental cost but a large effect on the ICER; this large effect on the ICER occurred when the additional benefit of celecoxib compared with other medications approached zero, resulting in a very large ICER. In contrast, the probability of responding to gabapentin was a key factor affecting the incremental costs with a relatively smaller effect on the ICER. Because gabapentin is required to be prescribed by specialists, lower response rates tend to reflect decreased usage by nonresponders and hence, lower incremental costs. Variation in the utility weights used and the pain scores had substantial effects on ICERs. Changes to other factors, such as the initial age and discount rates, had relatively little effect on results.

Overall, from examining both tornado diagrams, the important features of N-of-1 trials affecting the

Table 2 Variables used in the gabapentin/placebo model

Variable	Base-case value	Lower value	Upper value	Notes
Cost of trial				
Total fixed costs (\$)	23,200	11,800	39,600	Based on actual staff inputs and infrastructure costs
Variable cost per patient (\$)	1,322	802	1,600	
N participants	200	50	2,000	
Gabapentin responders (proportions)				
Gabapentin responders	0.244	0.083	0.392	Gabapentin/placebo N-of-1 trial; lower and upper 95% CI
Use gabapentin only	0.227	0.154	0.300	
Use gabapentin and other meds	0.603	0.406	0.799	
Use other meds only	0.170	0.161	0.180	
No meds	0.000	0.000	0.000	
Gabapentin nonresponders (proportions)				
Use gabapentin only	0.071	0.068	0.075	Gabapentin/placebo N-of-1 trial; lower and upper 95% CI
Use gabapentin and other meds	0.146	0.132	0.159	
Use other meds only	0.614	0.550	0.679	
No meds	0.169	0.161	0.176	
Gabapentin discontinuation rate (annual)	0.500	0.000	1.000	
No trial (proportions)				
Use gabapentin only	0.143	0.136	0.149	Assumed 100% greater than nonresponder
Use gabapentin and other meds	0.291	0.263	0.319	Assumed 100% greater than nonresponder
Use other meds only	0.566	0.601	0.435	Residual
No meds	0.000	0.000	0.097	Min from responders; high value = observed pretrial
Gabapentin discontinuation rate (annual)	0.250	0.000	0.500	
Other factors				
Cost of gabapentin (\$)	113.78	51.80	155.41	Calculated from observed daily doses over 12 months f/u, using PBS costs; lower and upper 95% CI
Cost of other meds (\$)	83.56	53.08	112.55	
Cost of gabapentin plus other meds (\$)	197.34	104.88	267.96	
Pain score gabapentin responder	3.64	3.03	4.24	Mean score of responders for periods of gabapentin use during trial; lower and upper 95% CI
Pain score gabapentin nonresponder	4.13	3.83	4.43	Mean score of nonresponders during trial; lower and upper 95% CI
Pain score no trial	4.29	4.03	4.54	Mean from all in trial; lower and upper 95% CI
Utility—gabapentin responder	0.74	0.53	0.96	Calculated from proportion with no, moderate, and extreme pain mapped to the EQ-5D
Utility—gabapentin nonresponder	0.71	0.68	0.75	
Utility—no trial	0.69	0.66	0.72	
Probability of death		Age-specific mortality rates		[15]
Start age (years)	57.6	41.8	73.4	Observed in trial; lower and upper 95% CI
Duration (months)	60	12	End of life	
Discount rate, % (annual)	5.00	0.00	10.00	[17]

CI, confidence interval.

ICER were the assumptions around the no-trial alternative (including the use of the intervention drug and other drugs, and the discontinuation rate). Changes in health outcomes, including the utility weights, were key factors, as was the probability the intervention drug was better than the comparator. Features of N-of-1 trials that were less important were the fixed costs, discount rates and the mix of drugs used by responders and nonresponders.

A scenario where prescribing of the high cost intervention medication is restricted to those who have shown a positive response in an N-of-1 trial would reduce the costs of the N-of-1 trial only; that is, the pain scores and QALYs would remain unchanged because the use of the medication in a nonresponder has no effect on these outcomes (Table 4). Thus, this restriction has some benefit to controlling pharmaceutical budgets and better use of medications.

The analysis of responders compared with nonresponders within the N-of-1 trial is used to identify

the incremental cost and cost-effectiveness of the intervention medication compared with the alternative medication (opposed to whether an N-of-1 trial provides value for money compared with no trial). The difference in medication costs for responders versus nonresponders in the celecoxib versus SR paracetamol trial were relatively small, whereas the difference in costs between responders and nonresponders in the gabapentin versus placebo trial were substantially greater (Table 5). In contrast, responders in the celecoxib trial had a slightly greater reduction in pain score compared with responders in the gabapentin trial. This difference in pain reduction translated into greater difference in QALYs between responders and nonresponders in the two trials. From this responder analysis for gabapentin, an ICER of \$8764 per point reduced on the pain scale and \$28,439 per QALY gained were obtained. For the celecoxib trial, ICERs were \$389 and \$522 per point of pain reduced and QALY gained, respectively.

Table 3 Results for the N-of-1 trial prescribing strategies: costs, outcomes and cost-effectiveness of the N-of-1 trials vs. no trial

	Gabapentin vs. placebo	Celecoxib vs. paracetamol
5 years (base case)		
Cost: no trial (\$)	5,654	1,193
Cost: N-of-1 (\$)	6,523	2,346
Incremental cost (\$)	869	1,152
Pain score: no trial	4.290	4.550
Pain score: N-of-1	4.012	4.437
Reduction in pain (points)	0.278	0.113
QALYs: no trial	3.141	3.045
QALYs: N-of-1	3.267	3.084
Incremental QALYs	0.126	0.039
Incremental cost per point reduction in pain (\$)	3,125	10,199
Incremental cost per QALY gained (\$)	6,896	29,550
12 months		
Cost: no trial (\$)	1,539	326
Cost: N-of-1 (\$)	2,722	1,592
Incremental Cost (\$)	1,183	1,267
QALYs: no trial	0.821	0.801
QALYs: N-of-1	0.853	0.811
Incremental QALYs	0.032	0.010
Incremental cost per point reduction in pain (\$)*	4,254	11,209
Incremental cost per QALY gained (\$)	36,958	126,661
End of life		
Cost: no trial (\$)	15,279	2,791
Cost: N-of-1 (\$)	15,893	3,809
Incremental Cost (\$)	614	1,018
QALYs: no trial	9.040	7.604
QALYs: N-of-1	9.396	7.703
Incremental QALYs	0.356	0.099
Incremental cost per point reduction in pain (\$)*	2,209	9,004
Incremental cost per QALY gained (\$)	1,725	10,278

*The pain score, obtained from the trials, is constant for all time horizons modeled. QALY, quality-adjusted life-year.

Discussion

This study provides important evidence that within the Australian context N-of-1 trials offer a realistic option for increasing patients' access to high-cost medications, under specific circumstances. In particular, the characteristics of the gabapentin trial appeared more economically viable than the celecoxib trial. Gabapentin is relatively more expensive than celecoxib, and

Table 4 Scenario where high-cost medication is available to N-of-1 responders only. Costs and cost per QALY gained compared with no trial over 5-years

	Gabapentin		Celecoxib	
	No trial	N-of-1	No trial	N-of-1
Cost (\$)	5,654	6,251	1,193	2,255
Incremental cost (\$)		597		1,062
QALYs	3.141	3.267	3.045	3.084
QALYs gained		0.126		0.039
ICER (\$)		4761		26,934

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.

Table 5 Results for the N-of-1 trial prescribing strategies: costs, outcomes and cost-effectiveness of gabapentin vs. placebo and celecoxib vs. paracetamol

	Gabapentin vs. placebo	Celecoxib vs. paracetamol
5 years (base case)		
Cost: nonresponder (\$)	5,512	2,301
Cost: responder (\$)	9,806	2,558
Incremental cost per responder (\$)	4,294	257
Pain score: nonresponder	4.130	4.550
Pain score: responder	3.640	3.890
Reduction in pain (points)	0.490	0.660
QALYs: nonresponder	3.230	3.000
QALYs: responder	3.381	3.492
Incremental QALYs	0.151	0.492
Incremental cost per point reduction in pain (\$)	8,764	389
Incremental cost per QALY gained (\$)	28,439	522
12 months		
Cost: nonresponder (\$)	2,515	1586
Cost: responder (\$)	3,391	1624
Incremental cost per responder (\$)	876	39
QALYs: nonresponder	0.841	0.789
QALYs: responder	0.891	0.918
Incremental QALYs	0.050	0.129
Incremental cost per point reduction in pain (\$)*	1,788	58
Incremental cost per QALY gained (\$)	17,525	298
End of life		
Cost: nonresponder (\$)	12,761	3,676
Cost: responder (\$)	26,067	4,454
Incremental cost per responder (\$)	13,306	778
QALYs: nonresponder	9.302	7.493
QALYs: responder	9.695	8.723
Incremental QALYs	0.393	1.230
Incremental cost per point reduction in pain (\$)*	27,156	1179
Incremental cost per QALY gained (\$)	33,859	633

*The pain score, obtained from the trials, is constant for all time horizons modeled. QALY, quality-adjusted life-years.

reducing its use in nonresponders results in greater cost-offsets compared with the cost-offsets obtained from reducing use of celecoxib in nonresponders. In addition, the proportion of responders in the gabapentin trial were greater than those in the celecoxib trial, and the reduction in pain score by gabapentin responders was greater than the pain reduction by celecoxib responders. Therefore, the gabapentin trial resulted in substantially greater QALYs than those obtained from the celecoxib trial.

Our analysis of the costs of developing, setting up and running N-of-1 trials showed a relatively high cost per individual trial. Nevertheless, the modeling suggests that these costs may partially recouped if the cost differential between the two therapies is sufficiently high, as illustrated by the gabapentin/placebo trials. In contrast, when the cost-differential is smaller, as in the celecoxib/SR-paracetamol trials, it was cheaper to allow every patient to use celecoxib. This concurs with

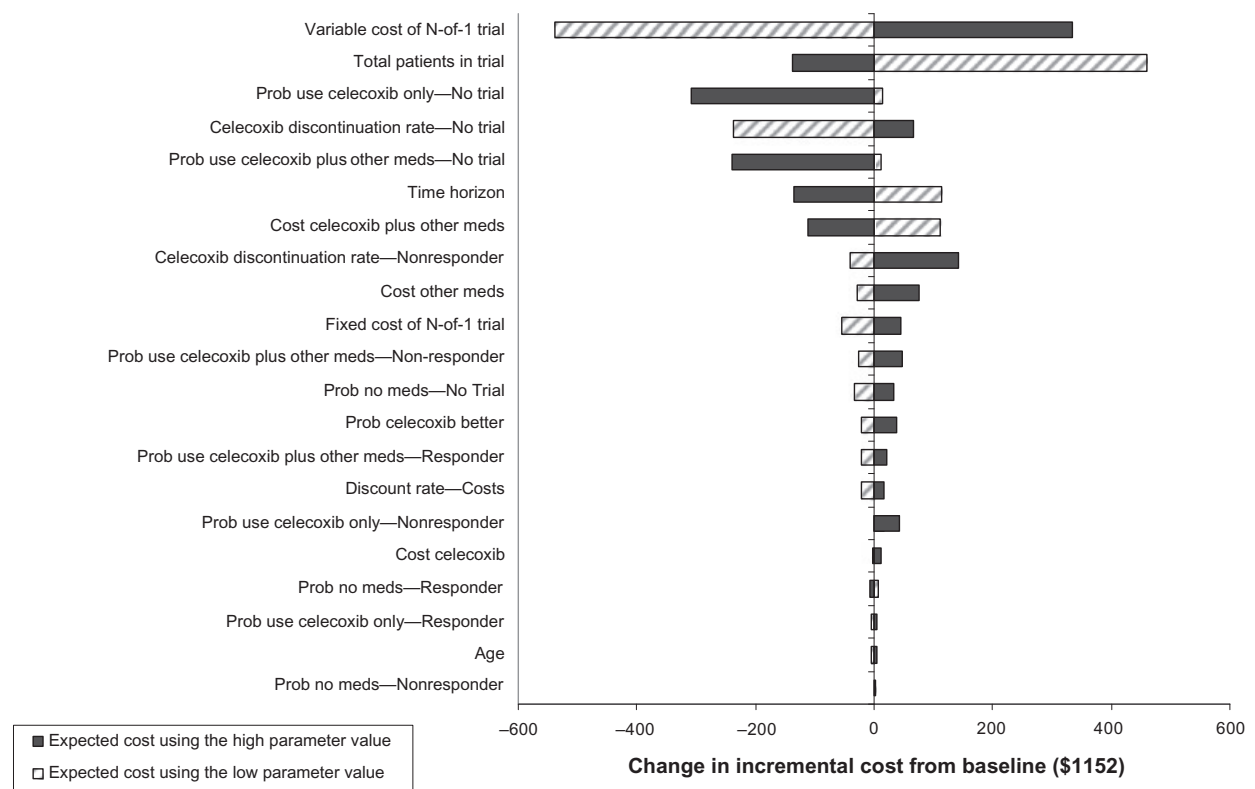


Figure 2 Sensitivity analysis around incremental costs for the celecoxib/paracetamol model. The baseline incremental cost of the “N-of-1 trial” compared with “No trial” was \$1152.

the findings of Pope et al. [8]. The additional costs of the N-of-1 trials reported here were \$869 and \$1152 for the gabapentin/placebo and celecoxib/paracetamol trials. Moreover, N-of-1 trials improve clinical and health outcomes. We estimated modest QALY gains of 3.8% and 1.3% for two trials, which when combined with costs, produced ICERs of \$6,896 and \$29,550 per QALY gained for the two trials. Nevertheless, over and above any costs or cost-offsets, there is value to both clinicians and patients in having knowledge that they are being prescribed medications to which they will respond positively, and thus, these analyses may understate the full economic benefit of N-of-1 trials.

Some of the assumptions chosen for the base-case models were simplifications and may be unlikely to be observed in the real world. For example, persistence with long-term therapy is generally poor (approximately 50%), particularly after the first 6 months [18]. Nevertheless, persistence is expected to be greater when the patient is given the knowledge that the medication is effective for them, and is expected to be much lower when the patients are told the medication does not work for them. A reduction in the number of responders persisting with the more expensive medication (or the duration of use by responders) would have the effect of reducing the ICERs (assuming quality of life was maintained). Conversely, a “leakage” effect of

nonresponders resuming the more expensive medication will reduce cost-effectiveness. The long-term rates of the opposing effects of persistence and leakage are unknown; however, we have attempted to capture these effects in our model using data reported from 12 months of follow-up.

Additional cost-offsets not included in our analysis may come from a reduction in physician time for medication review and treatment of adverse reactions for those in the N-of-1 trial; however, the size of this effect is unknown. Another limitation of the analysis is the need to extrapolate health outcomes from the 12-week trial for the modeled time horizon. In future, we recommend that follow-up data collection should include the clinical measures used to identify responders and the use of a utility instrument such as the EQ-5D. Similarly, the “No trial” group modeled in the analysis was, effectively, a hypothetical cohort. Ideally, testing the effectiveness and cost-effectiveness of N-of-1 trials requires participants to be randomized to standard care or an N-of-1 trial.

The method of patient selection for these trials may have affected response rates and therefore estimates of cost-effectiveness. Requests for the celecoxib/paracetamol trials were mostly patient-generated and therefore attracted people who were uncertain about the effectiveness of their medication. The gabapentin/

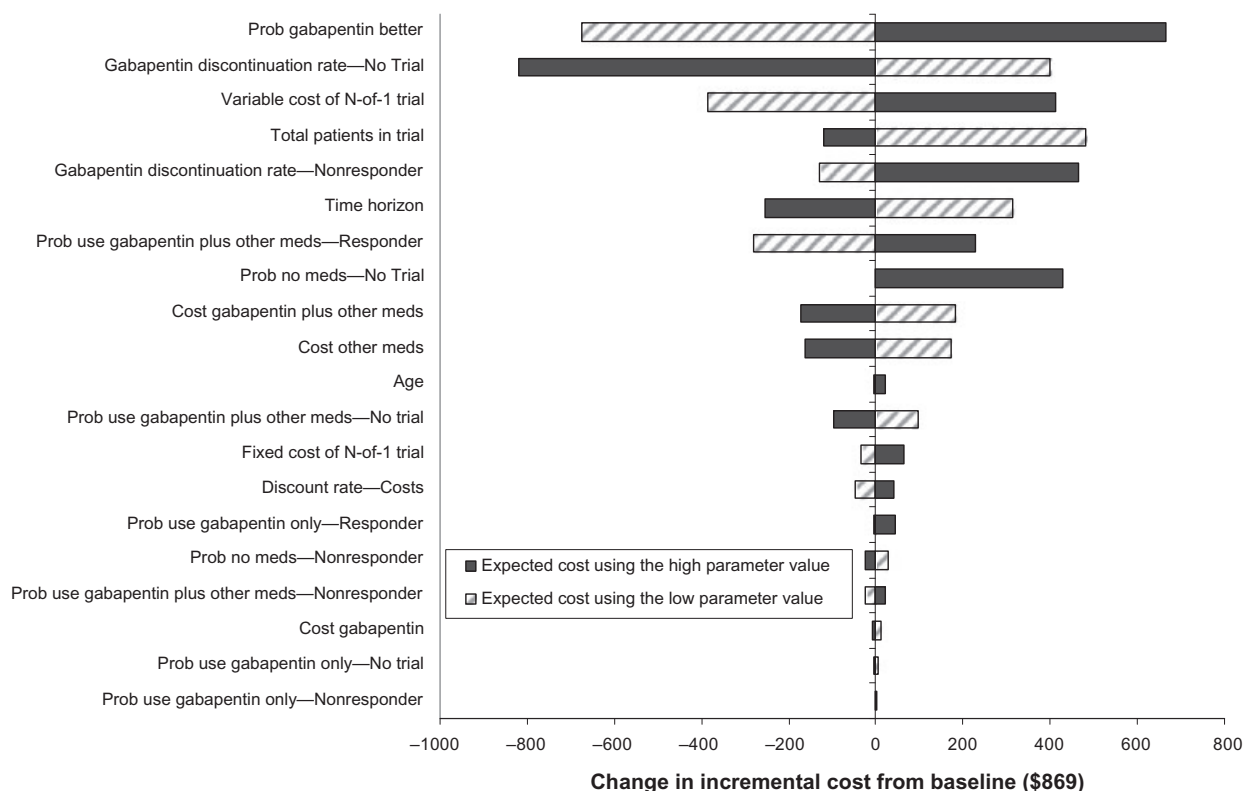


Figure 3 Sensitivity analysis around incremental costs for the gabapentin/placebo model. The baseline incremental cost of the “N-of-1 trial” compared with the “No trial” was \$869.

placebo trials were initiated by doctors who were uncertain of gabapentin’s effectiveness in patients on long-term gabapentin, who had shown some response to a 2- to 3-week trial of gabapentin.

The minimum and maximum doses used in the gabapentin trial were below those recommended for the treatment of neuropathic pain (900–3000 mg/day) [19]. Both of these factors could have reduced the number of responders. A lower number of responders results in lower total costs in the N-of-1 trial option. In turn, this requires a shorter duration of continuous treatment for the trial arm to become more cost-effective than the usual care arm.

The responder analysis, comparing the intervention medication with the set of “other medications,” is a spin-off benefit of N-of-1 trials. The responder analysis can allow efficacy, costs and cost-effectiveness of an intervention medication to be established and/or confirmed in addition to identifying the suitability of a medication for an individual. It is possible that non-random biases may occur in the N-of-1 trial process, despite double blinding, if patients know that the results will influence their treatment decisions. For example, patients may exaggerate benefits in the periods when they believe they are taking the more expensive medication [6].

Many of the practical issues of conducting post and telephone N-of-1 trials throughout Australia with minimal demands on prescribing doctors have been addressed by the N-of-1 trial service. Nevertheless, the trials were performed in relatively small numbers of consenting, motivated patients. The provision of trials in a timely fashion to large numbers of community or hospital patients would present considerable logistical challenges, but would not be impossible. One option would be an extension of the current authority-prescribing system, where doctors request approval for specific subsidized medications under a special authority. Funding of the extension of such a service could come from those who would benefit namely government, pharmaceutical companies and patients. Government stands to gain by making savings to the PBS budget. Pharmaceutical companies could benefit if the N-of-1 trials are a condition of listing for previously unlisted medications or if they are offered a premium price for medications in responders. That is, pharmaceutical companies could show a greater benefit by reporting the effect in responders compared with an alternative treatment. The price of the pharmaceutical could be increased to the point where the ICER was bordering on the acceptable threshold for government subsidy/funding, and thus, a higher price could be

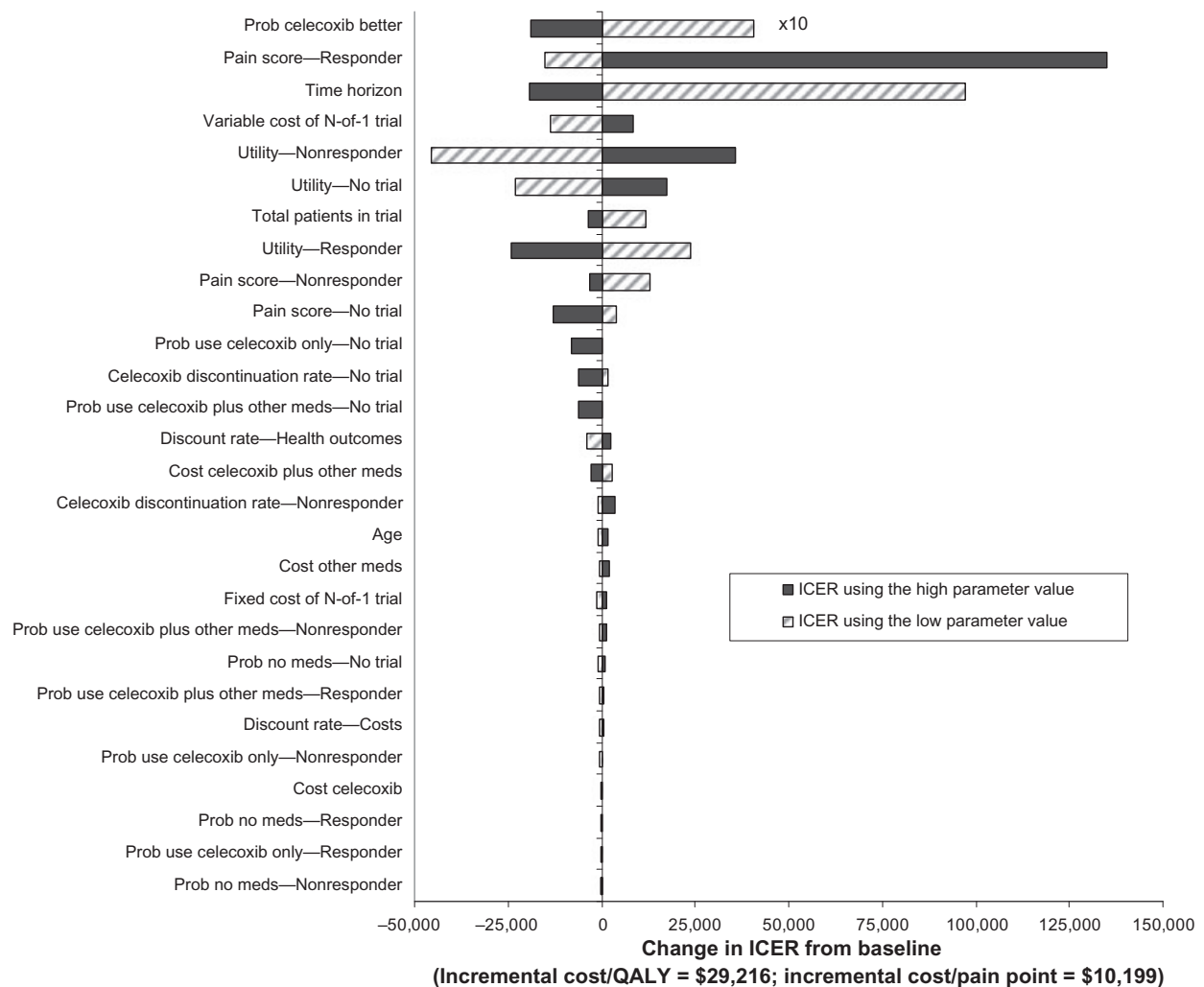


Figure 4 Sensitivity analysis around incremental cost per quality-adjusted life-year (QALY) gained for the celecoxib/paracetamol model. The baseline incremental cost-effectiveness ratio (ICER) of the “N-of-1 trial” compared with “No trial” was \$29,216.

obtained with the restriction that the medication is prescribed for responders only. Patients may benefit from clinical decisions based on individualized evidence; however, there may be strong resistance to pay for a test that may exclude them from taking a medication they think they need.

We analyzed a scenario where mandatory participation in an N-of-1 trial is a condition for getting affordable access to a desired medication and showed greater cost-offsets could be achieved; however, mandatory participation in an N-of-1 trial might also be considered a significant ethical or moral issue. An appeals mechanism might be necessary for those who refuse to consent to an N-of-1 trial, and for nonresponders disaffected by the denial of affordable access to medication. Furthermore, N-of-1 trials are double-blind studies for which informed consent is a standard requirement. Ethics guidelines state that refusal to consent to entry in a trial should never

compromise the doctor–patient relationship [20]. Nevertheless, clinicians commonly conduct informal (and methodologically inadequate) N-of-1 trials when they try a medication in a patient and judge a clinical response; and this occurs in the face of the issues outlined above.

Several questions remain unanswered about the broader application of N-of-1 trials. How can they be administered successfully in patients with cognitive impairment or for whom English is a second language? Should there be an item number or a Practice Incentive Payment for the effort required by doctors requesting them? Will they be accepted by doctors as a tool for rational prescribing or just perceived as another barrier to prescribing? Will they be accepted by patients who stand to lose affordable access to a medication that they may believe is helping them? A marketing campaign would be required to explain the benefits of N-of-1 trials as a tool for tailoring treat-

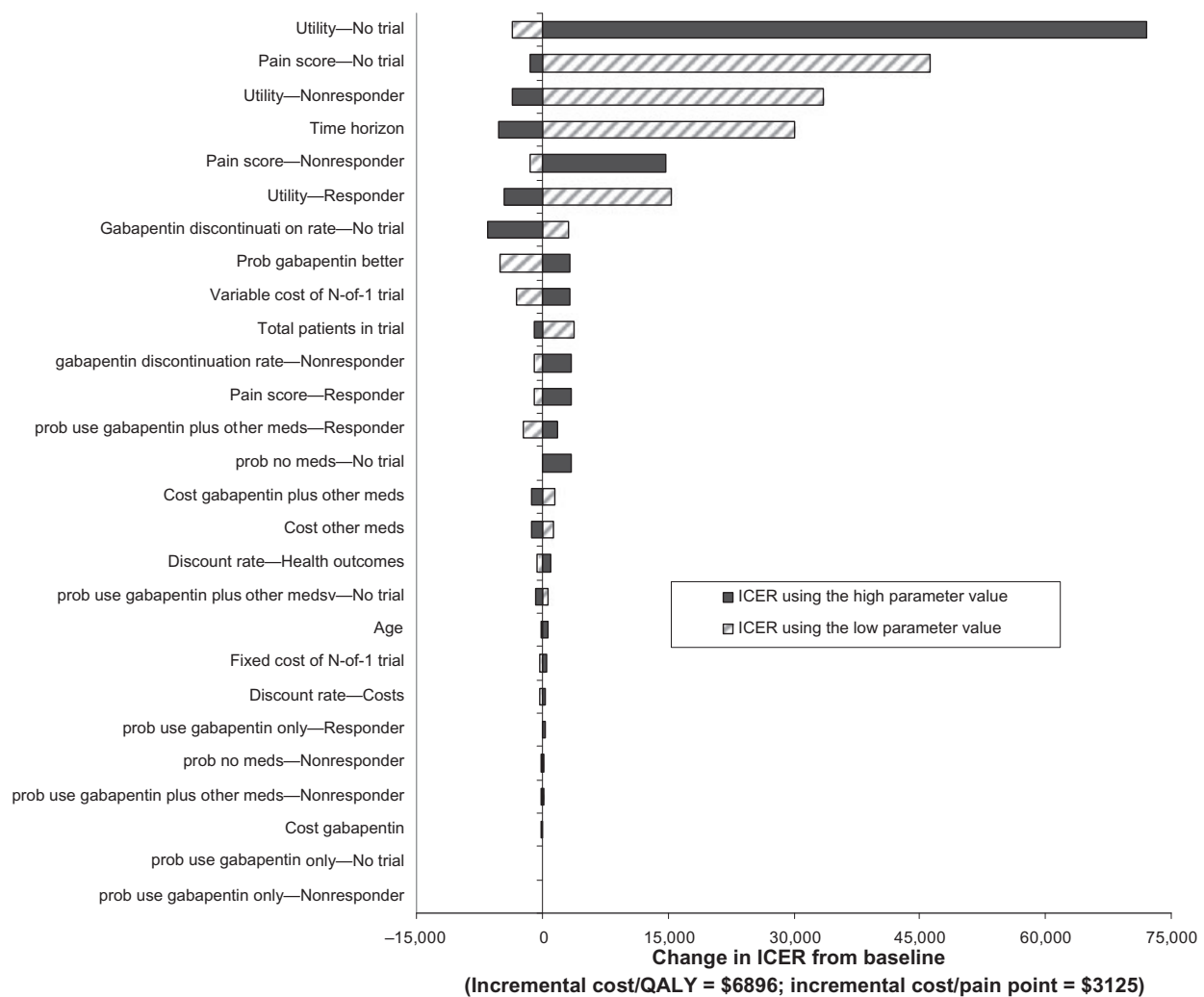


Figure 5 Sensitivity analysis around incremental cost per quality-adjusted life-year (QALY) gained for the gabapentin/placebo model. The baseline incremental cost-effectiveness ratio (ICER) of the “N-of-1 trial” compared with the “No trial” was \$6896.

ment to individual patients so these trials are not just seen as a method of cutting costs for the PBS.

Collectively, these issues restrict the range of medications suitable for an N-of-1 trial prescribing strategy (Table 6). Nevertheless, suitable medications would include expensive medications for the symptomatic

treatment of chronic conditions where there is a low overall response rate but a high and unpredictable variability in individual response. The difference in costs for responders and nonresponders is a key factor in being able to make cost-savings from conducting N-of-1 trials. If there is an alternative medication for nonresponders, it needs to be relatively cheap. N-of-1 trials may also have a role in targeting the use of medications that have a predictably superior clinical response to alternatives but with an unpredictably worse adverse event profile.

Table 6 Features of medications suited to an N-of-1 trial prescribing strategy

Pharmacological features	
Indicated for symptomatic treatment of chronic conditions	
Rapid onset of action	
Short washout period	
Clinical features	
Variable clinical response that cannot be predicted without a trial	
Superior clinical response to alternative but with a more serious adverse event profile	
Low overall response rate	
Other features	
High differential in price compared with alternatives	
Limited demand at a national level	

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